RESEARCH PAPER

Peri- and Post-operative Amplitude-integrated Electroencephalography in Infants with Congenital Heart Disease

JUAN GUI[1, 2], SHAORU HE[1, 2], JIAN ZHUANG[3], YUNXIA SUN[1], YUMEI LIU[1], SUIXIN LIANG[1], CHEN CHEN[1], YUAN REN[1], BI WANG[1] AND JIMEI CHEN[3]

From [1]Department of NICU, Guangdong General Hospital, Guangdong Academy of Medical Sciences; [2]The Second School of Clinical Medicine, Southern Medical University; and [3]Children's Heart Center, Guangdong Cardiovascular Institute; Guangzhou, Guangdong Province 510080, China.

Correspondence to: Dr Shaoru He,
Department of NICU,
Guangdong General Hospital,
Guangdong Academy of Medical
Sciences, No. 106, Zhongshan 2 Road,
Guangzhou, Guangdong Province
510515, China.
he_shaoru@yeah.net

Received: January 22, 2019;
Initial review: June 06, 2019;
Accepted: November 08, 2019.

Objective: To identify the factors influencing brain injury in infants with congenital heart disease (CHD) after cardiac surgery. **Methods:** This retrospective study investigated 103 infants with CHD undergoing cardiac surgery between January 2013 and February 2016. Pre- and postoperative amplitude-integrated electroencephalography (aEEG) recordings were assessed for background pattern, sleep-wake cycle pattern and seizure activity. Logistic regression model was used to determine the influencing factors of brain injury. **Results:** Pre-operatively, most infants in our study exhibited a normal background pattern, with 16.5% showing discontinuous normal voltage, whereas this pattern was observed in only 7.8% of infants postoperatively. The improvement in background pattern after surgery was significant ($P<0.05$) in infants at no more than 39 weeks of gestational age. Infants with postoperative sepsis or severe postoperative infection were prone to show a worse sleep-wake cycle pattern after heart surgery. **Conclusion:** The improvement in brain function of infants with CHD after cardiac surgery was associated with the gestational age and postoperative infection.

Keywords: *Cardiac surgery, Gestational age, Infection, Outcome*.

Congenital heart disease (CHD) is the most common birth defect, affecting approximately 1% of all live births [1]. With the tremendous improvement in treatment of CHD, the focus of attention has shifted toward managing brain injury, which is associated with neurodevelopment impairment affecting up to 50% of infants with CHD [2-4]. Because of the feasibility of continuous bedside monitoring brain activity, amplitude-integrated electroencephalography (aEEG) is increasing used to evaluate cerebral activity around infant cardiac surgery. Previously, aEEG was demonstrated as an early marker for brain injury in infants requiring cardiac surgery with CHD [5]. Although several factors including type of CHD, abnormalities of microstructural and metabolic brain development, and time of diagnosis have been identified as risk factors for brain injury [6,7], few studies have identified the predictors for brain function improvement or decline in infants with CHD undergoing cardiac surgery. Such predictors may help determine potential benefits or harm for brain function before operation.

METHODS

One hundred and three term infants who underwent surgery for CHD before 3 months of age between January 2013 and February 2016 at the NICU in our hospital were included in the study. Those infants who had any form of genetic or chromosomal abnormality independently associated with impaired neurodevelopment or were born before 37 weeks of gestational ages were excluded. The study was approved by the Ethics Committee of Guangdong General hospital, and written informed consent was obtained from all the parents.

Clinical data including Apgar scores, gestational age, birth weight, blood gas analysis, cardiovascular function, respiratory and multiorgan failure, neurological examination results, seizure occurrence, drug administration, neuroimaging data, infection, and surgical records were evaluated retrospectively for the study. Specifically, infection included postoperative sepsis diagnosed as bacterial infection by blood culture, and severe post-operative infection defined as postoperative infection (mainly pulmonary and urinary tract infections but not intracranial infection) that required antibiotics treatment, while excluding sepsis. Surgical procedures, cardiopulmonary bypass (CPB) time, and aortic cross-clamping (ACC) time were obtained from the surgical records.

aEEG was monitored 1 or 2 days before cardiac surgery and 3 or 7 days after surgery using an 8-channel EEG acquisition system (Nicolet One Monitor, Care Fusion, San Diego, California). The period of aEEG monitoring lasted for at least 24 hours each time and was extended when necessary. Eight disposable, self-adhesive EEG scalp electrodes (Blue Sensor BRS-50 K Ambu ECG electrode; Medicotest A/S, Ølstykke, Denmark) were applied in a reduced montage following the international 10-20 system. The 8-channel cross-brain aEEG trace was derived and displayed at 6 cm/hour on paper using a semi-logarithmic scale to assess and classify the aEEG background pattern. The channels were also used to record EEG data to describe episodes of EEG seizures in 10-second epochs. The 8-channel EEG recording was examined for the entire recording period when necessary. To ensure masking of evaluator, the expert who performed the main offline aEEG analyses was not involved in the clinical care of the infants.

The aEEG traces were classified by background voltage and descriptive pattern [8]. The aEEG recordings were categorized as continuous normal voltage (CNV) or discontinuous normal voltage (DNV). A combined third group called severe aEEG voltage pattern was defined, which included burst suppression, continuous low voltage, or a flat trace. We classified the Sleep-wake cycle (SWC) by occurrence into three types: normal SWC, immature SWC, and no SWC [9]. An electrographic seizure was defined as an evolving repetitive, stereotyped waveform with a definite onset, peak, and end that lasted for ≥10 seconds on raw EEG data [10]. Antiepileptic drugs were used to treat clinical seizures. Electrographic seizure activity was classified as no seizure, single attack (in which the amplitude of a single waveform appeared suddenly and showed persistent cerebral cortex activity) and recurrent attack (in which a recurring amplitude showed sudden and persistent cerebral cortex activity). Finally, we defined three types of pattern changes based on background pattern, SWC, and seizure activity by comparing to the preoperative traces: no change simply indicated the pattern did not alter, worse indicated the pattern shifted towards the abnormal type, and better denoted pattern shifted towards better type, e.g. from DNV to CNV. All reports were examined by qualified neonatal neurological experts.

Statistical analyses were performed using SPSS software, version 20 (IBM, Armonk,New York). Comparisons between groups were performed with the *t*-test, variance analysis or signed-rank test for continuous variables and with the x^2 test or Fisher's exact test for dichotomous variables. Comparisons of the ranked data were performed with the Wilcoxon sign-rank test. Logistic regression analysis was used to determine the influencing factors of aEEG. All values of *P* value <0.05 were considered statistically significant.

RESULTS

A total of 103 infants with CHD undergoing cardiac surgery were evaluated for the study. Demographic and clinical characteristics of all patients are shown in ***Table* I**. The mean (SD) gestational age at birth was 38.6 (2.4) weeks, while the mean age at surgery was 1.4 (1.2) months. The infants were classified into four types as previously defined, among which two-ventricle heart without arch obstruction was the predominant group (76, 73.8%), both two-ventricle heart with arch obstruction and single-ventricle heart without arch obstruction groups accounted for 12.6% of the total cases (*n*=13), and only one infant developed single-ventricle heart with arch obstruction. The comparison of pre- and postoperative aEEG results suggested that the background pattern was improved significantly after surgery (*P*=0.04) in infants of no more than 39 gestational weeks. The similar trends were observed for the SWC and seizure activity after surgery, but the differences were not statistically significant (***Table* II**). Since background patterns of only five infants turned worse after surgery, the changes in background pattern were classified as improved and not improved (including not changed and worse). Multivariate logistic regression analysis suggested that gestational age was the only factor affecting postoperative background pattern improvement (OR=0.20, 95% CI: 0.04-0.97; *P*=0.04), whereas bodyweight was not significant predictor for the improvement (***Table* III**). Infants with postoperative sepsis or severe postoperative infection were more likely to show a worsened SWC after heart surgery (OR=0.12, 95% CI: 0.02-0.67, *P*=0.02 and OR=6.77, 95% CI:1.60-28.68, *P*=0.01, respectively).

DISCUSSION

In the present study, background pattern of aEEG was improved in some infants after cardiac surgery, and the improvement was more likely to be identified in those with gestational age less than 39 weeks. Individuals with postoperative sepsis or severe infection were at increased risk of getting worse SWC after the operation. Our results demonstrate that gestational age and postoperative infection are predictive of benefits or harm after the surgery in terms of brain function.

Heart surgery may improve brain function of infants with CHD, as is indicated by the improvement of background pattern in some individuals. Several studies have demonstrated that normal background pattern of aEEG was observed in most infants preoperatively [11,12],

TABLE I Demographic and Clinical Characteristics of the Study Population (*N* = 103)

Characteristics	*No.* (%)
Male sex	41 (39.8)
*Gestational age, wk	38.6 (2.4)
*Birthweight, g	2936.5 (595.4)
*Age at surgery, mo	1.4 (1.2)
*Length of intensive care stay, d	27.2 (12.4)
Emergency operation	14 (13.6)
Corrective surgery	94 (91.3)
*Duration of CPB, min	92.3 (59.9)
*Aortic cross-clamp time, min	51.6 (40.1)
Delayed sternal closure	29 (28.2)
*Mechanical ventilation, d	7.0 (6.9)
CHD categories	
Two-ventricle heart without arch obstruction	76 (73.8)
Two-ventricle heart with arch obstruction	13 (12.6)
Single-ventricle heart without arch obstruction	13 (12.6)
Single-ventricle heart with arch obstruction	1 (1)
Preoperative background	
Normal	86 (83.5)
Mildly abnormal	17 (16.5)
Preoperative SWC	
Developed SWC	62 (60.2)
Immature SWC	41 (39.8)
Absent SWC	0
Preoperative seizure	
None	100 (97.1)
Single attack	1 (1.0)
Recurrent attack	2 (1.9)

*Data in no. (%) or *mean (SD); SWC: sleep-wake cycle; SS: single attack; RS: recurrent attack; CPB: Cardiopulmonary bypass; CHD: Congenital heart disease.*

TABLE II Changes between Pre- and Postoperative aEEG (*N*=103)

Changes of aEEG		*n (%)*
*Background pattern		0.04
Better	14 (13.59)	
No change	84 (81.55)	
Worse	5 (4.85)	
Sleep-wake cycle		0.52
Better	16 (15.5)	
No change	70 (67.9)	
Worse	17 (16.5)	
Seizure		0.86
Better	3 (2.91)	
No change	96 (93.2)	
Worse	4 (3.9)	

TABLE III Logistic Regression Analysis for Influencing Factors of Changes of Background Pattern and SWC

Change of aEEG	*Influencing factors*	*OR (95% CI)*
Improved background pattern		
Gestational age[#]	0.04	0.20 (0.04, 0.97)
Bodyweight[$]	0.23	0.35 (0.12, 1.04)
SWC no change	(0.02, 0.70)	
Postoperative septicemia[‡]	0.12	
Postoperative severe infection[**]	0.01	6.77 (1.60, 28.68)

*Gestational age ≤39 wks group as the reference group; body weight ≤3000 g group as the reference group; [‡]no postoperative septicemia group as the reference group; **postoperative severe infection group as the reference group.*

which was in line with our study. However, few studies have reported the improvement of background pattern after surgery. In fact, the occurrence of abnormal background pattern was increased after surgery in one study [13]. The differences should be interpreted with caution as the time for conducting aEEG monitoring was different and the sample size of both studies is relatively small.

We did not perform intra-operative aEEG monitoring in the study due to the unstable quality and lack of predictive value. Gunn K, *et al*. [14] found that aEEG background pattern will recover to the normal in most cases and there was considerable variability in the intraoperative pattern. Furthermore, postoperative but not intraoperative aEEG proved effective in identifying cerebral injury in infants with CHD [15].

Our study identified two factors that may help infer which individual would gain benefits or harm regarding brain function from cardiac surgery. Multiple risk factors, of preoperative, intraoperative, or postoperative, have been identified. Petit, *et al*. [16] reported that preoperative low arterial hemoglobin saturation was associated with transposition of the great arteries [16]. Cardiac arrest before surgery was found to increase risk of developing brain injury [6]. Prolonged total circulatory arrest during the operation was reported to be related to white matter brain injury [17]. Another study suggested that single ventricle physiology after the surgery was likely to increase risk of brain injury [18]. Our research focused on the changes of aEEG patterns and pinpointed two novel variables, namely gestational age and postoperative infection, as influencing factors for brain function, which may provide valuable insights for clinical practices.

What This Study Adds?

- Gestational age and postoperative infection are associated with changes in amplitude-integrated electroencephalography in infants with congenital heart diseases requiring cardiac surgery.

Our study had several limitations. Most importantly, the retrospective character limits the level of evidence. Sample size was small, which requires further validation of the findings. We did not systematically record intraoperative anesthetic use or report the effects of these drugs on outcomes. Lastly, long-term neurodevelopmental outcomes were not investigated.

In conclusion, we retrospectively correlated clinical factors with brain function measured by aEEG, highlighting gestational age and postoperative infection as predictors for improvement of cerebral function. If this is confirmed in larger prospective studies, it would help optimize and personalize the perioperative procedures for CHD to achieve better neurodevelopmental outcome.

Contributors: JG: study design and manuscript preparation; SRH, JZ, JMC: guarantor of integrity of the entire study; YXS: study concepts; YML,SXL: clinical studies; CC: statistical analysis; YR: data acquisition; BW: data analysis. All authors are approved to this manuscript.

Funding: This work was supported by the National Key Research and Development Plan Project (2018YFC1002600).

Competing Interest: None stated.

REFERENCES

1. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, *et al.* Birth prevalence of congenital heart disease worldwide a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58:2241-7.
2. Claessens NHP, Algra SO, Ouwehand TL, Jansen NJG, Schappin R, Haas F, *et al*. Perioperative neonatal brain injury is associated with worse school-age neurodevelopment in children with critical congenital heart disease. Dev Med Child Neurol. 2018;60:1052-8.
3. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, *et al*. Neurodevelopmental outcomes in children with congenital heart disease: Evaluation and management a scientific statement from the American Heart Association. Circulation. 2012;126:1143-72.
4. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, *et al*. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics. 2015;135:816-25.
5. Claessens NHP, Noorlag L, Weeke LC, Toet MC, Breur JMPJ, Algra SO, *et al*. Amplitude-integrated electroencephalography for early recognition of brain injury in neonates with critical congenital heart disease. J Pediatr. 2018;202:199-205.
6. Dimitropoulos A, McQuillen PS, Sethi V, Moosa A, Chau V, Xu D, *et al*. Brain injury and development in newborns with critical congenital heart disease. Neurology. 2013;81:241-8.
7. Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ, *et al*. Association of prenatal diagnosis of critical congenital heart disease with postnatal brain development and the risk of brain injury. JAMA Pediatr. 2016;170.
8. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103:1263-71.
9. Zhang L, Zhou YX, Li XF, Cheng TT. Hyperbilirubinemia influences sleep-wake cycles of term newborns in a non-linear manner. PloS One. 2017;12.
10. Shah NA, Wusthoff CJ. How to use: amplitude-integrated EEG (aEEG). Arch Dis Child Educ Pract Ed. 2015;100: 75-81.
11. Gunn JK, Beca J, Penny DJ, Horton SB, d'Udekem YA, Brizard CP, *et al*. Amplitude-integrated electroencephalography and brain injury in infants undergoing norwood-type operations. Ann Thorac Surg. 2012;93:170-6.
12. Toet MC, Flinterman A, van de Laar I, de Vries JW, Bennink GBWE, Uiterwaal CSPM, *et al*. Cerebral oxygen saturation and electrical brain activity before, during, and up to 36 hours after arterial switch procedure in neonates without pre-existing brain damage: Its relationship to neurodevelopmental outcome. Exp Brain Res. 2005; 165:343-50.
13. Latal B, Wohlrab G, Brotschi B, Beck I, Knirsch W, Bernet V. Postoperative amplitude-integrated electroencephalography predicts four-year neurodevelopmental outcome in children with complex congenital heart disease. J Pediatr. 2016;178:55-60.
14. Gunn JK, Beca J, Hunt RW, Olischar M, Shekerdemian LS. Perioperative amplitude-integrated EEG and neuro-development in infants with congenital heart disease. Intensive Care Med. 2012;38:1539-47.
15. Algra SO, Schouten AN, Jansen NJ, van Oeveren W, Haas F, Groenendaal F, *et al*. Perioperative and bedside cerebral monitoring identifies cerebral injury after surgical correction of congenital aortic arch obstruction. Intensive Care Med. 2015;41:2011-2.
16. Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, *et al*. Preoperative Brain Injury in Transposition of the Great Arteries Is Associated With Oxygenation and Time to Surgery, Not Balloon Atrial Septostomy. Circulation. 2009;119:709-16.
17. Beca J, Gunn JK, Coleman L, Hope A, Reed PW, Hunt RW, *et al*. New white matter brain injury after infant heart

surgery is associated with diagnostic group and the use of circulatory arrest. Circulation. 2013;127:971-9.

18. McQuillen PS, Barkovich AJ, Hamrick SEG, Perez M, Ward P, Glidden DV, *et al*. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke. 2007;38:736-41.